

INFORMATION DISCLOSURE
STATEMENT BY APPLICANT

(use as many sheets as necessary)

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of



JAN 23 2004

Complete if Known

Application Number	10/075,097
Filing Date	02/13/2002
First Named Inventor	Nnochiri N. Ekwuribe
Group Art Unit	1654
Examiner Name	Anish Gupta
Attorney Docket Number	9233-46

Sheet

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of

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U.S. PATENTS AND PATENT PUBLICATIONS

Examiner Initials*	Cite No.	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY
		Number	Kind Code (if known)		
ADL	1	US-5,889,153		Suzuki et al.	03/30/1999

OTHER NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	
ADL	2	Aoki et al. "Chronic Intermittent Intravenous Insulin Therapy: A New Frontier in Diabetes Therapy" <i>Diabetes Technology & Therapeutics</i> 3(1):111-123 (2001)	
	3	Clement, Stephen "A Dose-Escalation Study of the Effects of Two Sequential Doses of Oral Modified Insulin on Blood Glucose Concentrations in Patients with Type 1 Diabetes Mellitus" <i>American Diabetes Association Annual Meeting</i> (June 25, 2001) (Poster)	
	4	Francis et al. "Polyethylene Glycol Modification: Relevance of Improved Methodology to Tumour Targeting" <i>Journal of Drug Targeting</i> 3:321-340 (1996)	
	5	Guzman et al. "Effects of Fatty Ethers and Stearic Acid on the Gastrointestinal Absorption of Insulin" <i>PRHSJ</i> 9(2):155-159 (1990)	
	6	International Search Report, PCT/US02/04440, 12/23/2003	
	7	Lindsay et al. <i>The Acetylation of Insulin Biochem J.</i> 121:737-745 (1971)	
	8	Liu et al. "Glucose-Induced Release of Glycosylpoly(ethylene glycol) Insulin Bound to a Soluble Conjugate of Concanavalin A" <i>Bioconjugate Chem.</i> 8:664-672 (1997)	
	9	Mesih et al. "Hypoglycaemic effect of oral insulin preparations containing Brij 35, 52, 58 or 92 and stearic acid" <i>J. Pharm. Pharmacol.</i> 33:733-734 (1981)	
	10	Michael et al. "Loss of Insulin Signaling in Hepatocytes Leads to Severe Insulin Resistance and Progressive Hepatic Dysfunction" <i>Molecular Cell</i> 6:87-97 (1999)	
	11	Moghaddam, Amir "Use of polyethylene glycol polymers for bioconjugations and drug development" <i>American Biotechnology Laboratory</i> pp. 42, 44 (July 2001)	
	12	Neubauer et al. "Influence of Polyethylene Glycol Insulin on Lipid Tissues of Experimental Animals" <i>Diabetes</i> 32:953-958 (October 1983)	
	13	Puskas et al. "Investigation f Chymotrypsin Digestion Profile of Orally Active Insulin Conjugate Him2" <i>AAPSPharmSci</i> 3(3) (2001) (Abstract)	
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	15	Shen et al. "(C) Means to Enhance Penetration; (3) Enhancement of polypeptide and protein absorption by macromolecular carriers via endocytosis and transcytosis" <i>Advanced Drug Del. Reviews</i> 8:93-113 (1992)	
	16	Sindelar et al. "A Comparison of the Effects of Selective Increases in Peripheral or Portal Insulin on Hepatic Glucose Production in the Conscious Dog" <i>Diabetes</i> 45:1594-1604 (1996)	
	17	Sirokman et al. "Refolding and proton pumping activity of a polyethylene glycol-bacteriorhodopsin water-soluble conjugate" <i>Protein Science</i> 12:1161-1170 (1993)	
	18	Torchilin, Vladimir P. "Immunoliposomes and PEGylated Immunoliposomes: Possible Use for Targeted Delivery of Imaging Agents" <i>Immunomethods</i> 4:244-258 (1994)	
	19	Wei et al. "A Poly(Ethylene Glycol) Water-soluble Conjugate of Porin: Refolding to the Native State" <i>Biochemistry</i> 34:6408-6415 (1995)	
	20	Xia et al. "Effects of polyoxyethylene chain length distribution on the interfacial properties of polyethylene glycol n-dodecyl ether" <i>Yingyong Huaxue</i> 2(4): 59-65 (1985) (Abstract)	
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Examiner Signature

A handwritten signature in black ink, appearing to read "M. S. Ekwuribe".

Date Considered

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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FORM PTO-1449 U.S. Department of Commerce Patent and Trademark Office				Attorney Docket Number 9233-46			Serial No. 10/075,097
LIST OF DOCUMENTS CITED BY APPLICANT (Use several sheets if necessary)				Applicants: Ekwuribe et al.			
				Filing Date February 13, 2002		Group 1654 1646	
U. S. PATENT DOCUMENTS							
Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate
ANL	1.	2002/0160938	10/31/2002	Brandenburg et al.	A1		
ANL	2.	2003/0144468	07/31/2003	Ekwuribe et al.	A1		
	3.	2003/0087808	05/08/2003	Soltero et al.	A1		
	4.	2003/0083232	05/01/2003	Soltero et al.	A1		
ANL	5.	2003/0069170	04/10/2003	Soltero et al.	A1		
ANL	6.	2003/0060606	03/27/2003	Ekwuribe et al.	A1		
	7.	2003/0050228	03/13/2003	Ekwuribe et al.	A1		
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	19.	5,364,838	11/15/1994	Rubsamen	A		
	20.	5,420,108	05/30/1995	Shohet	A		
	21.	5,468,727	11/21/1995	Phillips et al.	A		
	22.	5,597,797	01/28/1997	Clark et al.	A		
ANL	23.	5,681,567	10/28/1997	Martinez et al.	A		

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ADR	24.	5,704,910	01/06/1998	Humes	A		
↑	25.	5,714,519	02/03/1998	Cincotta et al.	A		
	26.	5,763,396	06/09/1998	Weiner et al.	A		
	27.	5,843,866	12/01/1998	Weiner et al.	A		
	28.	5,866,584	02/02/1999	Cincotta et al.	A		
	29.	5,997,848	12/07/1999	Patton et al.	A		
	30.	6,042,822	03/28/2000	Gilbert et al.	A		
	31.	6,057,292	05/02/2000	Cunningham et al.	A		
	32.	6,147,108	11/14/2000	Hauptman	A		
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		36. 99/65941	12/23/1999	WO	A1		

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↑	38.	Allaudeen et al. "Orally Active Insulin: A Single Insulin Conjugate Selected for Future Studies" 60 th Annual Meeting of the American Diabetes Assoc., Atlanta, GA June 2000 (Abstract)
	39.	Anderson et al. "HIM2, a Novel Modified Insulin, has Improved Systemic Pharmacokinetics in Normal Dogs, Compared to Unmodified Insulin" American Diabetes Association 62 nd Annual Meeting June 2002 (Abstract)
	40.	Block, Lawrence H. "Pharmaceutical Emulsions and Microemulsions" <i>Pharmaceutical Dosage Forms: Disperse Systems</i> , Vol. 2, Ed. Lieberman et al. (1996) p 47-109
↓	41.	Bone et al. "Successful Treatment of an Insulin Dependent Rat Model of Human Type I Diabetes with Orally Active Insulin" Program and Abstracts, 4 th International Workshop on Lessons from Animal Diabetes, Omiya, Japan November 1994 (Abstract)
ADR	42.	Bone et al. "Successful Treatment of Type 1 Diabetes with Orally-Active Insulin: Studies in The Insulin Dependent BB/S Rat" Program and Abstracts, 55 th Annual Meeting of the American Diabetes Association, Atlanta Georgia, June 1995 (Abstract)

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LIST OF DOCUMENTS CITED BY APPLICANT			
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<p style="text-align: right;">O I P F JC109 NOV 26 2003 U. S. PATENT & TRADEMARK OFFICE</p> <p>Applicants: Ekwuribe et al.</p>			
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<p>43. Brange and Volund "Insulin Analogs with Improved Pharmacokinetic Profiles" <i>Advanced Drug Delivery Reviews</i> 35:307-335 (1999)</p> <p>44. Cleland et al. "Emerging Protein Delivery Methods" <i>Current Opinion in Biotechnology</i> 12:212-219 (2001)</p> <p>45. Clement et al. "Effects of Multiple Doses of Orally Administered Hexyl Insulin M2 (HIM2) on Postprandial Blood Glucose (PPG) Concentrations in Type 1 Diabetic (T1) Patients" American Diabetes Association 62nd Annual Meeting, June 2002 (Poster)</p> <p>46. Clement et al. "Oral Insulin Product Hexyl-Insulin Monoconjugate 2 (HIM2) in Type 1 Diabetes Mellitus: The Glucose Stabilization Effects of HIM2" <i>Diabetes Technology & Therapeutics</i> 4(4):459-466 (2002)</p> <p>47. Clement, Stephen "A Dose-Escalation Study of the Effects of Two Sequential Doses of Oral Modified Insulin on Blood Glucose Concentrations in Patients with Type 1 Diabetes Mellitus" American Diabetes Association Annual Meeting (June 25, 2001) (Abstract)</p> <p>48. Damge et al. "Poly(alkyl cyanoacrylate) Nanospheres for Oral Administration of Insulin" <i>Journal of Pharmaceutical Sciences</i> 86(12):1403-1409 (Dec. 1997)</p> <p>49. Dandona et al. "Effect of an Oral Modified Insulin on Blood Glucose Levels in Fasting and Fed Type 1 Diabetic Patients Receiving a "Basal" Regimen of Injected Insulin" American Diabetes Association Annual Meeting (June 25, 2001) (Abstract)</p> <p>50. Ekwuribe et al. "Calcitonin Drug-Oligomer Conjugates, and Uses Thereof" U.S. Serial No. 10/166,355, filed 11/08/2002, including Preliminary Amendment dated 02/26/2003 and Supplemental Preliminary Amendment dated 03/31/2003</p> <p>51. Ekwuribe et al. "Mixtures of Drug-Oligomer Conjugates Comprising Polyalkylene Glycol, Uses Thereof, and Methods of Making Same" U.S. Serial No. 09/873,797, filed 06/04/2001</p> <p>52. Ekwuribe et al. "Oral Insulin Delivery: Hydrolyzable Amphiphilic Oligomer Conjugates Prolong Glucose Reduction" <i>Proceed. Int'l. Symp. Control. Rel. Bioact. Mater.</i> 26:147-148 (1999)</p> <p>53. Ekwuribe, Nnochiri "Conjugation-Stabilized Polypeptide Compositions, Therapeutic Delivery and Diagnostic Formulations Comprising Same, and Method of Making and Using the Same" <i>Biotechnology Advances</i> 14(4):575-576 (1996) (Abstract)</p> <p>54. Hinds et al. "Synthesis and Characterization of Poly(ethylene glycol)-Insulin Conjugates" <i>Bioconjugate Chem.</i> 11:195-201 (2000)</p> <p>55. Kipnes et al. "Control of Postprandial Plasma Glucose by an Oral Insulin Product (HIM2) in Patients with Type 2 Diabetes" <i>Emerging Treatments and Technologies</i> 26:2 (2003)</p> <p>56. Kipnes et al. "The Effects of an Oral Modified Insulin on Postprandial Blood Glucose Levels in Patients with Type 2 Diabetes" American Diabetes Association Annual Meeting (June 24, 2001) (Abstract)</p> <p>57. Kipnes et al. "The Effects of an Oral Modified Insulin on Postprandial Blood Glucose Levels in Patients with Type 2 Diabetes Mellitus" American Diabetes Association Annual Meeting (June 24, 2001) (Poster)</p> <p>58. Kube, D.M. "Multitalented Proteins Play a Key Role in Therapeutics" <i>Genomics and Proteomics</i> (Sept. 2002)</p> <p>59. Marschutz et al. "Oral Peptide Drug Delivery: Polymer-Inhibitor Conjugates Protecting Insulin from Enzymatic Degradation In Vitro" <i>Biomaterials</i> 21:1499-1507 (2000)</p> <p>60. Musabayane et al. "Orally Administered, Insulin-Loaded Amidated Pectin Hydrogel Beads Sustain Plasma Concentrations of Insulin in Streptozotocin-Diabetic Rats" <i>Journal of Endocrinology</i> 164:1-6 (2000)</p> <p>61. Pang, David C. "Bridging Gaps in Drug Discovery and Development" <i>Pharmaceutical Technology</i> 82-94 (Nov. 1998)</p>			

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LIST OF DOCUMENTS CITED BY APPLICANT (Use several sheets if necessary)			
Applicants: Ekwuribe et al.			
Filing Date February 13, 2002			Group 1654 1646
1	2	Pauletti et al. "Improvement of Oral Peptide Bioavailability: Peptidomimetics and Prodrug Strategies" <i>Advanced Drug Delivery Reviews</i> 27:235-256 (1997)	
3	4	63. Puskas et al. "Investigation of Chymotrypsin Digestion Profile of Orally Active Insulin Conjugate HIM2" <i>AAPS Pharm. Sci.</i> 3(3) 2001 (Abstract)	
5	6	64. Radhakrishnan et al. "Chemical Modification of Insulin with Amphiphilic Polymers Improves Intestinal Delivery" <i>Proceed. Intl. Symp. Control. Rel. Bioact. Mater.</i> 25:124-125 (1998) (Abstract)	
7	8	65. Radhakrishnan et al. "Oral Delivery of Insulin: Single Selective Modification at B29-LYS With Amphiphilic Oligomer" Program and Abstracts, 1999 National Meeting of the Ameri. Assoc. Pharm. Scient., New Orleans, LA (1999) (Abstract)	
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13	14	68. Richards et al. "Self-Association Properties of Monomeric Insulin Analogs Under Formulation Conditions" <i>Pharmaceutical Research</i> 15(9):1434-1441 (1998)	
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17	18	70. Sluzky et al. "Kinetics of Insulin Aggregation in Aqueous Solutions Upon Agitation in the Presence of Hydrophobic Surfaces" <i>Proc. Natl. Acad. Sci.</i> 88:9377-9381 (Nov. 1991)	
19	20	71. Soltero et al. "Insulin Polypeptide-Oligomer Conjugates, Proinsulin Polypeptide-Oligomer Conjugates and Methods of Synthesizing Same" U.S. Serial No. 10/382,022, filed 03/05/2003	
21	22	72. Soltero et al. "Pharmaceutical Compositions of Drug-Oligomer Conjugates and Methods of Treating Diseases Therewith" U.S. Serial No. 10/382,069, filed 03/05/2003	
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25	26	74. Song et al. "Direct Measurement of Pulsatile Insulin Secretion from the Portal Vein in Human Subjects" <i>Journal of Clinical Endocrinology & Metabolism</i> 85(12):4491-4499 (2000)	
27	28	75. Still and McAllister "Effects of Orally Active Modified Insulin in Type 1 Diabetic Patients" <i>Clinical Pharmacol. Therap.</i> 69(2): P95 (Feb. 2001) (Abstract)	
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33	34	78. Still et al. "Magnitude and Variability of Pharmacokinetic and Glucodynamic Responses to Modified Human Insulin Administered Orally to Healthy Volunteers" <i>Diabetes Research and Clinical Practice</i> 56:S77 (2002)	
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37	38	80. Still, J. Gordon "Development of Oral Insulin: Progress and Current Status" <i>Diabetes/Metabolism Research and Reviews</i> , 18(1):S29-S37 (2002)	

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LIST OF DOCUMENTS CITED BY APPLICANT			
<p>Q Use several sheets if necessary)</p> <p><i>JAN 13 2003</i></p> <p><i>50157</i></p> <p><i>PATENT & TRADEMARK OFFICE</i></p>			
Applicants: Ekwuribe et al.			
Filing Date: 02/13/02			Group <i>1646 1654</i>

U. S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date if Appropriate
<i>AK</i>	1.	3,919,411	11/11/75	Glass et al.			
	2.	3,256,153	06/14/66	Heimlech			
	3.	3,868,356	02/25/75	Smyth			
	4.	3,950,517	04/13/76	Lindsay et al.			
	5.	4,003,792	01/18/77	Mill et al.			
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	7.	4,087,390	05/02/78	Shields			
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	10.	4,179,337	12/18/79	Davis et al.			
	11.	4,229,438	10/21/80	Fujino et al.			
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<i>AK</i>	25.	4,717,566	01/05/88	Eckenhoff et al.			

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U.S. PATENT DOCUMENTS (CONT.)						
53	26.	4,744,976	05/17/88	Snipes et al.		
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1654						
ADJL	54.	5,324,775	06/28/94	Rhee et al.		
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LIST OF DOCUMENTS CITED BY APPLICANT <i>(Use several sheets if necessary)</i>				Applicants: Ekwuribe et al.	
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140.	EP 0 031 567	07/08/81	EPO			Yes	
141.	JP 1 254 699	10/11/89	Japan			No	
142.	WO 93/01802	02/04/93	PCT			Yes - abstract	
143.	WO 95/09831	04/13/95	PCT			Yes	
144.	EP 0 483 465	08/02/95	EPO			Yes - claims	
145.	WO 95/30641	11/16/95	PCT			Yes	
146.	EP 0 597 007	10/16/96	EPO			Yes	
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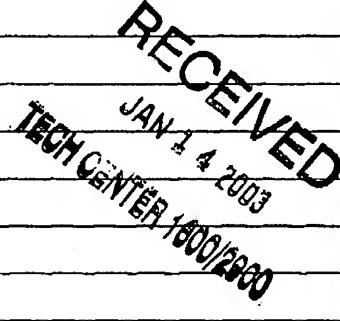
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LIST OF DOCUMENTS CITED BY APPLICANT		JAN 14 2003 TEC... 1654/2003	
<p style="text-align: center;">(Use several sheets if necessary)</p> <p style="text-align: center;">JAN 13 2003 1654/2003</p> <p style="text-align: center;">PATENT & TRADEMARK OFFICE</p>		Applicants: Ekwuribe et al.	
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